Please add claim 24 as follows:

C2 A4

24. The method according to claim 1 wherein said gel matrix comprises one or more basement membrane proteins selected from the group consisting of laminin, collagen, fibrin, nidogen and heparin sulfate proteoglycan.

REMARKS

A. Amendments to the Claims

Upon entry of the present amendments, claims 4 and 6-9 will be pending in the above-identified application. The amendments to the claims are supported throughout the specification, including the claims as originally filed. More particularly, subparts (e) and (f) of claim 4 have been amended to be consistent with subpart (c) therein. Claim 6 has been amended to correct an improper antecedent basis with respect to claim 4. The amendment to claim 8 is supported by the specification as originally filed at page 72, lines 18 and claim 8 as originally filed because one skilled in the art would recognize Matrigel to be a composition of basement membrane proteins. New claim 9 depends from claim 8 and recites a Markush group of basement membrane proteins supported by the material spanning page 72, lines 18-20 of the specification as originally filed.

The foregoing amendments have changed the language of the claims in a manner that continues to identify the subject matter of the claims as methods of screening for modulators of cell migration using members of the family of Cysteine-rich ECM polypeptides (e.g. Cyr61 and Fisp12), without altering the scope of said claims. Accordingly, the present amendments neither introduce new matter nor alter the scope of the claims.

B. Outstanding Rejections

Claims 5, 6 and 8 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

1. **Rejection of Claim 5 Under 37 C.F.R. § 1.75(c) Should Be Withdrawn.**

The Examiner objected to claim 5 under 37 C.F.R. § 1.75(c) for being of improper independent form for failing to limit the subject matter of a previous claim. In view of its cancellation, the Applicant respectfully submits that the rejection of claim 5 under 37 C.F.R. § 1.75(c) should be withdrawn.

2. **Rejection of Claims 5 and 6 Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn.**

Dependent claims 5 and 6 were rejected under 35 U.S.C. § 112, second paragraph, for a lack of antecedent basis for the limitation "said first and second fibroblast cells." The Applicant traverses the rejection in view of the cancellation of claim 5 and the foregoing amendments to claim 6 which amends the limitation to read "said fibroblast cells", which is consistent with independent claim 4. In view of the foregoing comments, the Applicant respectfully submits that the rejection of claims 5 and 6 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

3. **Rejection of Claim 8 Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn.**

Claim 8 was rejected under 35 U.S.C. § 112, second paragraph, for containing the trademark "Matrigel" as a limitation. The Applicant traverses the rejection in view of the foregoing amendment to claim 8 which replaced "Matrigel" with a description of the gel which comprises basement membrane proteins, which is supported by the specification as originally filed. (see page 72, lines 18-21, of the specification) In view of this amendment, the Applicant submits that the rejection of claim 8 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

C. Patentability Arguments

1. **The Rejection of Claims 4-8 Under 35 U.S.C. §103(a) Over Iwamoto in View of Lind and either (a) Yang or (b) O'brien and Bork, Should be Withdrawn.**

Claims 4-8 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Iwamoto *et al.* (hereinafter, "Iwamoto") in view of Lin *et al.* (hereinafter, "Lin") and either (a) Yang or (b) O'Brien *et al.* (hereinafter, "O'Brien") and Bork. In response, the Applicant

respectfully submits that the rejection is improper on the grounds that a person of ordinary skill in the art would not have had a reasonable expectation of success at arriving at the claimed invention from combining Iwamoto with Lin and either (a) Yang or (b) O'Brien and Bork.

The Examiner characterized the invention as a method drawn to (i) a method of screening for a modulator of cell migration comprising forming test and control gel matrices (ii) of Cyr61, (iii) a suspected modulator of cell migration and (iv) one of Matrigel, collagen or fibrin, seeding human fibroblast cells (v) presenting $\alpha 6\beta 1$ integrin (vi) onto the test and control matrices, incubating the fibroblast cells, measuring the levels of migration in the test and control matrices by visual inspection, and comparing the levels of cell migration, whereby a modulator of cell migration is identified by its ability to alter the level of cell migration in the test matrix compared to the control matrix.

a. Iwamoto

The Examiner characterized Iwamoto as disclosing a method of screening for a modulator of cell migration comprising forming test and control gel matrices (part (i)), of a chemoattractant (part (iii)), and of Matrigel, layering transformed fibroblast cells onto the matrices (part (iv)), incubating the cells, and measuring the levels of cell migration by microscopic inspection, and using the assay for testing factors which inhibit tumor cell migration *in vitro* as a screen for compounds with the potential to inhibit tumor cell invasion *in vivo* (part (vi)). The Examiner characterized Lin as disclosing that $\alpha_6\beta_1$ is abundantly expressed in all neoplastically transformed fibroblast cell lines (part (v)). A combination of the above characterizations of Iwamoto and Lin yields every part of the claimed invention, except for the use of Cyr61 as a chemoattractant (part (ii)). In arriving at the claimed invention, the Examiner incorrectly points to either (a) Yang or (b) O'Brien and Bork for the teaching that Cyr61 is a chemoattractant.

b. Yang

The Examiner alleged that Yang discloses that (i) Cyr61 is a member of a family of cysteine rich proteins known to be chemoattractants, mitogens and proto-oncoproteins, and (ii) Cyr61 has chemoattractant activity. The Applicant respectfully submits that the Examiner has overstated the teachings of Yang. With regards to the activity of Cyr61, Yang states as follows:

> Cyr61 is a member of a family of proteins that absolutely conserve the 38 cysteines and have a putative signal peptide. Other Cyr61 family members have been shown to be chemoattractants, mitogens and proto-oncogenes. ... Initial functional analysis of Cyr61 has shown that it can suppress foci formation in NIH 3T3 cells. We have also found a chemoattractant activity in serum stimulated NIH3T3 cells that *may be* related to Cyr61. Further work will be aimed at refining our knowledge of how Cyr61 and its family members may function in biological processes.

See Yang (emphasis added). The above language from Yang is merely speculation that Cyr61 may have chemoattractant activity, based in part on the observation that some members of the family of cysteine rich proteins have been shown to acts as chemoattractants, mitogens and proto-oncoproteins. One of ordinary skill in the art would characterize Yang as the findings are summarized therein: "further work" is necessary to determine "how Cyr61 and its family members may function in biological processes." *See* ¶ 1, last sentence. The leap between the author's speculation that serum stimulation induces chemoattractant activity and the assignment of that activity to Cyr 61 is speculation and represents at best and in the author's own terms, a suggestion that further work be undertaken and is not a proper basis for a finding of obviousness.

c. O'Brien and Bork

The Examiner combined the teachings of O'Brien and Bork to arrive at the conclusion that Cyr61 is a chemoattractant. The Examiner characterizes O'Brien as disclosing that (i) *cyr61* is a growth factor-inducible immediate early gene which encodes a member of a family of growth factors comprising Cyr61, Fisp12, and CTGF, and (ii) CTGF possesses mitogenic and chemotactic activities. The Examiner characterizes Bork as disclosing that all of the members of the family of growth regulators comprising CTGF, Fisp12, and Cyr61 have most of their molecular functions in common and that functional information provided for one member can be transferred to other proteins of the family. The Examiner concludes, therefore, that Bork suggests that the chemoattractant function of CTGF described by O'Brien can be attributed to Cyr61. The critical citation from Bork relied on by the Examiner is as follows:

> Because of the high level of sequence similarity among the members of the CCN family, they probably have most of their molecular functions in common. Thus functional information provided for one member can be transferred to other proteins of the family. For example, *cyr61* is known to interact with both cell

> surfaces and the extracellular matrix, and it binds heparin with high affinity. Similar binding activities can be anticipated for other family members, whereas specific interactions such as binding of CTGF to a defined PDGF receptor *might* be a unique feature of [CTGF].

See Bork, page 126, left-hand column (emphasis added; references omitted).

The Applicants respectfully submit that the Examiner has mischaracterized the combined teachings of O'Brien and Bork. The disclosure of Bork merely speculates that the members of the family of growth regulators comprising CTGF, Fisp12, and Cyr61 (the "CCN family") have some molecular functions in common. There is no indication in Bork that members of the CCN family have all molecular functions in common. It also acknowledges that they have unique features. In fact, Bork highlights several **differences** between the molecular function of members of the CCN family as follows:

> [I]n adult *nov* is found in large amounts in lung and brain, bu in embryos it is only expressed in kidney. *fisp-12* has an expression pattern similar to *cyr61* and is also abundant in adult lung. However, this is still 10-20 times lower than in stimulated cells. The expression of *cyr61* during embryogenesis has been studied more detailed and has been mainly assigned to the developing cartilaginous skeleton.

See Bork, p. 126. One of ordinary skill in the art would characterize the teachings of Bork as the findings are summarized therein:

> Although equivalent structural modules in different proteins might have distinct functions, the characterization of the modular architecture narrows the range of possibilities for the structure and function of the CCN family. A final proof for the functional suggestions, of course, can only be obtained by experiments.

See Bork, p. 129-130. In light of the speculation by Bork, the combined the teachings of Bork and O'Brien are nothing more than an invitation to try to determine what the biological function of Cyr61 is. Such an invitation to further experimentation is not a proper basis for finding an invention obvious and, therefore, the applicants respectfully request that the rejection be withdrawn.

d. C mbination of Iwamot and Lind and either (a) Yang r (b) O'Brien and Bork

The Examiner alleged that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used Cyr61 as an alternative chemoattractant in the cell invasion assay taught by Iwamoto, because (a) Yang and (b) O'Brien with Bork teach that Cyr61 is a chemoattractant. The Applicant respectfully submits that the Examiner has incorrectly concluded what one of ordinary skill in the art would have reasonably believed, at the time of the invention, about the biological properties of Cyr61. As mentioned above, (a) Yang and (b) O'Brien and Bork merely state that Cyr61 may be a chemoattractant.

The speculation of (a) Yang and (b) O'Brien and Bork that Cyr61 may be a chemoattractant is based solely on the fact that database sequence analysis identified Cyr61 as a member of the family of cysteine-rich secreted proteins and that a single members of this newly identified family of proteins (CTGF and its orthologs) was known to be a chemoattractant. Based on (a) Yang or (b) O'Brien and Bork, one of ordinary skill in the art would not conclude that Cyr61 was a chemoattractant because of the inherent uncertainty of assigning biological function based on sequence alignment, especially when the biological function of only one protein is known. For example, Zmasek and Eddy state the following:

> Most proteins belong to families that consist of subfamilies with different biological functions. This complicates efforts to infer the function of newly sequenced proteins.
>
> Pairwise search algorithms (BLAST, FASTA) tend to classify novel sequences too aggressively. Recognizing the first representative of a novel functional subfamily - often an extremely interesting result - tends to require expert human intuition about how similar two sequences should be if they indeed have the same biological role.

See Zmasek and Eddy, page 1, left-hand column (attached as Appendix B).

The Applicant respectfully submits that the Examiner is either using impermissible hindsight based on the discoveries set forth in the present application or using the impermissible standard of "obvious to try" to conclude that one of ordinary skill in the art would have used Cyr61 as an alternative chemoattractant in the cell invasion assay taught by Iwamoto. At the time the invention was made, Cyr61 was not known to be a chemoattractant. In fact, Yang and Bork,

themselves acknowledged that further work would be necessary to determine the biological function of Cyr61. Therefore, it would not have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used Cyr61 as an alternative chemoattractant in the cell invasion assay taught by Iwamoto. In view of the foregoing, the Applicant respectfully submits that that the rejection of claims 4-8 under 35 U.S.C. § 103(a) is improper and should be withdrawn.

CONCLUSION

In view of the above amendments and remarks, the Applicant respectfully submits that the instant application is in good and proper order for allowance. Early notification of this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite this prosecution of the instant application, the Examiner is encouraged to call the undersigned at (312) 902-5464.

Respectfully submitted,

KATTEN MUCHIN ZAVIS

By: _____
David W. Clough, Ph.D.
Registration No. 36,107

Dated: February 26, 2002
KATTEN MUCHIN ZAVIS
525 W. Monroe Street, Suite 1600
Chicago, IL 60661
Telephone: (312) 902-5464

APPENDIX A

Pursuant to 37 C.F.R. §1.121(c)(1)(ii), Applicant presents herewith marked-up text of the claims of this application as amended by the foregoing amendment.

4. (Amended) A method for screening a modulator of cell migration comprising the steps of:

   (a) forming a gel matrix comprising Cyr61 and a suspected modulator of cell migration;

   (b) preparing a control gel matrix comprising Cyr61;

   (c) seeding fibroblast cells presenting an $\alpha_6\beta_1$ integrin onto the gel matrix of step (a) and the control gel matrix of step (b);

   (d) incubating said fibroblast cells;

   (e) measuring the levels of cell migration by inspecting the interior of [said] the gel matrix of step (a) and [said] the control gel matrix of step (b) for cells;

   (f) comparing the levels of cell migration measured in step (e), whereby a modulator of cell migration is identified by its ability to alter the level of cell migration in the gel matrix of step (a) when compared to the level of cell migration in the control gel matrix of step (b).

6. (Amended) The method according to claim 4 wherein said [first and second] fibroblast cells comprise a heparin sulfate proteoglycan.

8. (Amended) The method according to claim 4 wherein said gel comprises matrix [is comprised of] basement membrane proteins [selected from the group consisting of Matrigel, collagen, and fibrin].

24. (New) The method according to claim 4 wherein said gel matrix comprises one or more basement membrane proteins selected from the group consisting of laminin, collagen, fibrin, nidogen and heparin sulfate proteoglycan.